Amendments to the Drawings:

Please enter the attached replacement drawings for Figs. 1A, 1B, 2A and 2B. A mark-up showing the changes is attached.

Attachment: Replacement Sheet
Annotated Sheet Showing Changes

REMARKS

Replacement drawings are provided for Figs. 1A and 1B and 2A and 2B. The replacement drawings differ from the previous version in that the first amino acid of the mature region of the variable regions is shown double underlined. Such is in conformance with the informal drawings originally filed in the parent case, a copy of which are attached. The double underlining was inadvertently omitted in formalizing the drawings.

Claims 14 and 15 have been amended to specify that the claimed immunoglobulins specifically bind to gamma interferon, as described in the specification at p. 8, lines 35-37. Claim 17 has been amended to specify that heavy chain position H11 is the equivalent position of the mouse AF2 antibody, as in other claims. Claim 18 has been amended to recite SEQ ID NOS. for the EU immunoglobulin. An *In re Hawkins* declaration relating to the incorporation of these SEQ ID NOS. is attached. Support for new claims 25 and 26 is provided by original claim 8 in combination with p. 8, lines 19-32 and p. 12, lines 12-14.

Applicants use the paragraph numbering of the office action in responding to the Examiner's remarks.

3. The Examiner alleges that the removal of the word "mature" from the Brief Description of Figures 2A and 2B changes the scope of the description and constitutes new matter. Applicants respectfully disagree. Amendment of the specification to conform to the figures does not constitute new matter. MPEP 2163.06. The amino acid sequences shown in Fig. 2A and 2B either are, or are not, mature sequences, as a matter of a scientific fact. In fact, they are not mature sequences. Such can be readily recognized by comparing the sequences with the mature heavy chain humanized sequence disclosed in Fig. 3 of the application, or the mature humanized light chain sequence disclosed in Fig. 32A of WO 92/11018 (which lacks the first twenty amino acids of Fig. 2A). Such is also shown by the double underlining of the first amino acid of the mature protein in the originally filed informal drawings (which has now been restored in the amended formal drawings). Applicants offer to define the mature variable region as starting at the double underlined residue if the Examiner prefers it. In any event, given that the sequences in Figs. 2A and 2B are not just mature variable regions, but rather variable regions including

signal sequences, the proposed amendment simply conforms the brief description of Figs. 2A and 2B to what is shown in the figures and does not constitute new matter.

6-7. Claims 17 and 21-23 are alleged to lack enablement on the basis that undue experimentation would be require to produce variants of the exemplified properties. In response, it is submitted that the specification provides considerable guidance for producing variants of the exemplified humanized antibodies retaining specific affinity for γ-interferon. The specification identifies amino acids occupying CDR positions and a limited number of variable framework residues that interact with CDRs or are otherwise relatively intolerant of variance (see specification at e.g., pp. 18-19). Immunoglobulins having a number of permutations of substitutions at these positions are exemplified (SEQ ID NOS. 8-11), and other optional substitutions are proposed (p. 20, lines 1-4). The specification indicates that the remaining framework residues are relatively tolerant of change (p. 20, lines 6-12). The specification further teaches that these residues are not selected at random but rather are obtained entirely or substantially from the variable framework region of a human antibody (p. 18, lines 24-30). The specification also teaches that other human antibodies besides EU can be used as a source of framework residues, particularly those of subgroup I. (p. 18, lines 30-35). The framework residues in such antibodies have collectively survived the forces of evolution in providing a framework for a human antibody, and are likely to be able to fulfill this same role at least to some degree to confer specific binding at non-critical positions of a mouse antibody.

The Examiner correctly notes that the specification teaches that additional substitutions beyond those specifically identified in the application can be tolerated but are not preferred, but incorrectly construes such teaching as detrimental to enablement. The specification's disclosure that the exemplified sequences are preferred teaches the artisan that there is no need to make variants of exemplified sequences, but does not imply that the artisan would be unable to do so.

The Examiner also cites Chen as teaching as teaching that 20 of 46 point mutations in an antibody were nonfunctional, and that combinations of mutations increased the proportion of nonfunctional antibodies. However, all of Chen's mutations were in a CDR region, and of the 15 single mutations, only one lacked binding affinity. Of the pairs of two mutations, 42% retained

binding affinity. These results show that even within the CDR regions, the probability of a single point mutations causing lack of binding is very low. The probability would be even lower for mutations in the variable region frameworks. These results show that one would easily be able to generate numerous variants of the exemplified sequences retaining affinity with a high expectation of success. Although the probability declines for combinations of mutations, the probabilities of Chen for random mutations in the CDR are not representative of combinations of mutations in the variable region frameworks. Thus, the artisan would still expect a substantial number of variants in the variable region frameworks to retain binding affinity, particularly if the substitutions are predominantly conservative substitutions following the teaching of the specification.

The Examiner also alleges that all of the amino acids in a particular CDR can be substituted. However, insofar as substituting all residues of a CDR would cause loss of specific binding, the resulting antibody would no longer be included with the amended claims.

The test of enablement is not whether some amino acid substitutions cause loss of binding affinity, but whether a reasonable number of analogs retaining binding affinity could be routinely made based on the teaching of the specification. Here, there would have been no technical difficulty in constructing large families of nucleic acids encoding antibody chains retaining all or most of the residues indicated to be relatively intolerant of change and containing variation in other positions. Some of the variants thereby produced might lack specific binding and in some instances, the lack of specific binding might appear unpredictable in view of the nature of substitution that was performed. Nevertheless, it would be virtually certain that many substitutions of noncritical variable region framework residues, particularly conservative substitutions, would lead to retention of specific binding, as would use of alternative sources of framework residues to the EU antibody. Using the phage display method disclosed in the specification at paragraph bridging pp. 11-12 millions of variants can be screened simultaneously for binding to gamma interferon, optionally in competition with an exemplified humanized antibody (see specification at p. 9, linese 19-22). Using this methods millions of nucleic acids encoding different variants can be cloned into a phage display vector and screened simultaneously. Because many antibodies with specific binding would be present in the initial

library, and the phage display method efficiently screens antibodies having a desired specificity, one would expect to isolate a reasonable number of antibodies with the desired specificity from such a screening. Particularly, if some variants screened included framework residues from human antibodies other than EU, the requirement of 90% sequence identity recited in the claims is a comparatively modest assessment of the extent of divergence likely to be present in selected sequences. Therefore, it is submitted that based on the teaching of the specification, one could produce a reasonable number of variants of the exemplified antibody sequences without undue experimentation.

The facts and circumstances are analogous to those in the leading Federal Circuit case on enablement, *In re Wands,* 858 F.2d 731 (Fed. Cir. 1988). The issue in Wands was whether the specification of the Wands patent enabled production of a class of antibodies having IgM isotype and a binding affinity of at least 10^9 M^{-1} using Kohler Milstein technology. As the Examiner is aware, Kohler Milstein technology is a classical technique that involves individualized screening of hybridomas to identify a subset with desired binding characteristics. Until the hybridomas have been screened, it is unpredictable which will have the desired characteristics. Nevertheless, the court found that "practitioners of this art are prepared to screen negative hybridomas in order to find one that makes the desired antibody" 858 F.2d at 740, and that the patent was held to be enabled.

Here, where variants of an exemplified humanized antibody can be screened using phage display, the need for experimentation is still further reduced. The phage-display method permits simultaneous randomization and mass selection of desired characteristics. By contrast, in the *Wands* case antibodies were produced by immunization and analyzed by individualized screening for desired binding characteristics. For these reasons, it is submitted that the present claims were submitted for at least the same reasons as those in *Wands*.

8. Claims 17 and 21-23 are rejected under 35 USC 112, first paragraph based on alleged lack of written description. It alleged (citing to *Eli Lilly v. University of California*) that the specification does not disclose representative species, and only describes the required function and not the structure of the claimed antibodies. This rejection is respectfully traversed.

In *Lilly*, the Federal Circuit held that a claim directed to nucleic acids encoding human insulin (a hitherto uncloned human protein) lacked written description in the absence of actual sequence data for a nucleic acid encoding human insulin. The *Lilly* court also found that generic claims to cDNA encoding vertebrate or mammalian insulin lacked written description because:

> a generic statement such as "vertebrate insulin cDNA" or "mammalian insulin cDNA," without more is not an adequate written description of the genus because it does not distinguish the claimed genus form others, except by function. It does not specifically define any of the genes that fall within its definitions. It does not define any structural features commonly possessed by members of the genus that distinguish them from others. One skilled in the art therefore cannot, as one can do with a fully described genus, visualize or recognize the identity of the members of the genus. A definition by function, as we have previously indicated does not suffice to define the genus because it is only an indication of that the gene does, rather than what it is.
>
> 43 USPQ2d at 1406.

The present facts and circumstances are considerably different from those in Lilly. Here, applicants have defined humanized immunoglobulins by structural features commonly possessed by members of the genus that distinguishes them from others: that is, the requirement for 90% sequence identity to SEQ ID NO. 8 and the requirement that position H11 be occupied by a residue from the mouse AF2 antibody. The skilled artisan can also readily visualize or recognize the identify of any member falling within the structural formula and can readily test the same to determine whether it has the required specific binding. By contrast, in *Lilly*, no sequence was described and it was not possible to visualize any members of the claimed genus nor to distinguish them from other sequences except by function.

Because applicants have described the claimed genus by a structural property that distinguishes the claimed immunoglobulins from all other materials, it is respectfully submitted the strong presumption that the specification as filed provides written description (MPEP 2163 at p. 2100-156, second column) has not been overcome.

9. Claims 14-23 stand rejected under 35 USC 112, first paragraph on the basis that the recitation of a "mature light chain region" in claims 14, 15 and 17 constitutes new matter. This rejection is respectfully traversed.

The recitation of a humanized mature light chain in claim 17 has explicit support in claim 6 as filed and should not present any issues of new matter.

With respect to claims 14 and 15, the Examiner appears to be taking the position that applicants were in possession of mouse antibody AF2 having the full length variable regions of SEQ ID NO:2 and 4, but not of mouse antibody AF2 having the mature regions of SEQ ID NOS: 2 and 4 without the signal sequences. As explained above, SEQ ID NOS:2 and 4 inherently contain signal sequences, which would be processed when the mouse AF2 antibody is actually expressed, leaving the mature regions. The mature regions of mouse AF2 had already been published as evidenced by Figs. 30A and B of WO92/10018 and the legend thereto at p. 15. As is apparent from the experiment shown in Fig. 4 of the present application, applicants were in possession of expressed mouse antibody AF2, which would inherently have the mature variable regions of SEQ ID NOS: 2 and 4. Thus, applicants were in possession of an antibody having mature variable regions of SEQ ID NOS: 2 and 4.

Whether WO92/10018 is incorporated into the present specification is irrelevant to the issue of possession. WO92/10018 simply illustrates that the mature regions of the mouse AF2 antibody were known in the art, and thus generally in possession of those skilled in the art. The present application shows that applicants were in possession of expressed mouse AF2 antibody, and hence its mature variable regions.

10-11. Applicants provide a terminal disclaimer over the cited patent.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 650-326-2400.

Respectfully submitted,

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Attachments
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Annotated Sheet
Showing Changes


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ATGGAATCACAGACTCTGGTCTTCATATCCATACTGCTCTGGTTATATGGTGCTGATGGG
 M  E  S  Q  T  L  V  F  I  S  I  L  L  W  L  Y  G  A  D  G

AACATTGTTATGACCCAATCTCCCAAATCCATGTACGTGTCAATAGGAGAGAGGGTCACC
 N  I  V  M  T  Q  S  P  K  S  M  Y  V  S  I  G  E  R  V  T

TTGAGCTGCAAGGCCAGTGAAAATGTGGATACTTATGTATCCTGGTATCAACAGAAACCA
 L  S  C  K  A  S  E  N  V  D  T  Y  V  S  W  Y  Q  Q  K  P

GAGCAGTCTCCTAAACTGCTGATATATGGGGCATCCAACCGGTACACTGGGGTCCCCGAT
 E  Q  S  P  K  L  L  I  Y  G  A  S  N  R  Y  T  G  V  P  D

CGCTTCACGGGCAGTGGATCTGCAACAGATTTCACTCTGACCATCAGCAGTGTGCAGGCT
 R  F  T  G  S  G  S  A  T  D  F  T  L  T  I  S  S  V  Q  A

GAAGACCTTGCAGATTATCACTGTGGACAGAGTTACAACTATCCATTCACGTTCGGCTCG
 E  D  L  A  D  Y  H  C  G  Q  S  Y  N  Y  P  F  T  F  G  S

GGGACAAAGTTGGAAATAAAG
 G  T  K  L  E  I  K
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FIG. 1A

```
ATGGGATGGAGCTGTATCATCCTCTTCTTGGTAGCAACAGCTACAGGTGTCCTCTCCCAG
 M  G  W  S  C  I  I  L  F  L  V  A  T  A  T  G  V  L  S  Q

GTCCAACTGCAGCAGCCTGGGGCTGACCTTGTGATGCCTGGGGCTCCAGTGAAGCTGTCC
 V  Q  L  Q  Q  P  G  A  D  L  V  M  P  G  A  P  V  K  L  S

TGCTTGGCTTCTGGCTACATCTTCACCAGCTCCTGGATAAACTGGGTGAAGCAGAGGCCT
 C  L  A  S  G  Y  I  F  T  S  S  W  I  N  W  V  K  Q  R  P

GGACGAGGCCTCGAGTGGATTGGAAGGATTGATCCTTCCGATGGTGAAGTTCACTACAAT
 G  R  G  L  E  W  I  G  R  I  D  P  S  D  G  E  V  H  Y  N

CAAGATTTCAAGGACAAGGCCACACTGACTGTAGACAAATCCTCCAGCACAGCCTACATC
 Q  D  F  K  D  K  A  T  L  T  V  D  K  S  S  S  T  A  Y  I

CAACTCAACAGCCTGACATCTGAGGACTCTGCGGTCTATTACTGTGCTAGAGGATTTCTG
 Q  L  N  S  L  T  S  E  D  S  A  V  Y  Y  C  A  R  G  F  L

CCCTGGTTTGCTGACTGGGGCCAAGGGACTCTGGTCACTGTCTCTGCA
 P  W  F  A  D  W  G  Q  G  T  L  V  T  V  S  A
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FIG. 1B

```
ATGGAGACCGATACCCTCCTGCTATGGGTCCTCCTGCTATGGGTCCCAGGATCAACCGGA
 M  E  T  D  T  L  L  L  W  V  L  L  L  W  V  P  G  S  T  G

GATATTCAGATGACCCAGTCTCCGTCGACCCTCTCTGCTAGCGTCGGGGATAGGGTCACC
 D  I  Q  M  T  Q  S  P  S  T  L  S  A  S  V  G  D  R  V  T

ATAACCTGCAAGGCCAGTGAAAATGTGGATACTTATGTATCCTGGTATCAGCAGAAGCCA
 I  T  C  K  A  S  E  N  V  D  T  Y  V  S  W  Y  Q  Q  K  P

GGCAAAGCTCCCAAGCTTCTAATTTATGGGGCATCCAACCGGTACACTGGGGTACCTTCA
 G  K  A  P  K  L  L  I  Y  G  A  S  N  R  Y  T  G  V  P  S

CGCTTCAGTGGCAGTGGATCTGGGACCGATTTCACCCTCACAATCAGCTCTCTGCAGCCA
 R  F  S  G  S  G  S  G  T  D  F  T  L  T  I  S  S  L  Q  P

GATGATTTCGCCACTTATTACTGCGGACAGAGTTACAACTATCCATTCACGTTCGGTCAG
 D  D  F  A  T  Y  Y  C  G  Q  S  Y  N  Y  P  F  T  F  G  Q

GGGACCAAGGTGGAGGTCAAACGT
 G  T  K  V  E  V  K  R
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FIG. 2A

```
ATGGGATGGAGCTGGATCTTTCTCTTCCTCCTGTCAGGTACCGCGGGCGTGCACTCTCAG
 M  G  W  S  W  I  F  L  F  L  L  S  G  T  A  G  V  H  S  Q

GTCCAGCTTGTCCAGTCTGGGGCTGAACTCAAGAAACCTGGGAGCTCCGTGAAGGTCTCC
 V  Q  L  V  Q  S  G  A  E  L  K  K  P  G  S  S  V  K  V  S

TGCAAAGCTTCTGGCTACATCTTTACTAGCTCCTGGATAAACTGGGTAAAGCAGGCCCCT
 C  K  A  S  G  Y  I  F  T  S  S  W  I  N  W  V  K  Q  A  P

GGACAGGGTCTCGAGTGGATTGGAAGGATTGATCCTTCCGATGGTGAAGTTCACTACAAT
 G  Q  G  L  E  W  I  G  R  I  D  P  S  D  G  E  V  H  Y  N

CAAGATTTCAAGGACAAGGCTACACTTACAGTCGACAAATCCACCAATACAGCCTACATG
 Q  D  F  K  D  K  A  T  L  T  V  D  K  S  T  N  T  A  Y  M

GAACTGAGCAGCCTGAGATCAGAGGACACTGCAGTCTATTACTGTGCAAGAGGATTTCTG
 E  L  S  S  L  R  S  E  D  T  A  V  Y  Y  C  A  R  G  F  L

CCCTGGTTTGCTGACTGGGGCCAAGGAACCCTGGTCACAGTCTCCTCAG
 P  W  F  A  D  W  G  Q  G  T  L  V  T  V  S  S
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FIG. 2B